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Outcome of ICU treatment in invasive aspergillosis

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Abstract *Objective:* To assess the outcome of intensive care treatment in invasive aspergillosis.
Design: Retrospective study.
Setting: University Hospital, Medical Intensive Care Unit (ICU).
Patients: Twenty-five patients with invasive aspergillosis who were admitted to the medical ICU in a $5\frac{1}{2}$ year period. Twenty-two had received high-dose chemotherapy for (mainly hematologic) malignancies, one had been treated with cyclosporine and prednisolone for systemic lupus erythematosus, one with high-dose methylprednisolone for polyarteritis nodosa and one had an ARDS after near-drowning.
Measurements and results: The medical records were reviewed for patient and disease characteristics, outcome, reasons for admission to the ICU, supportive care and antifungal therapy as well as for the results of cultures and autopsy. Out of 25 patients, a definite ante mortem diagnosis could be established in seven. When autopsied patients were included, a total of 15 suffered from proven invasive aspergillosis. Although standard antifungal treatment and maximal available supportive care were given, 23 of 25 patients (92%) died after a mean of 15 (1–51) days in the ICU. Both patients who recovered had received high-dose chemotherapy for hematologic malignancy and showed bone marrow recovery and/or had a localized pulmonary infection.
Conclusions: In patients with highly suspected or proven invasive aspergillosis, admission to an ICU and mechanical ventilation should be considered in cases of localized infection and obvious signs of hematologic recovery. In most other circumstances ICU admission for mechanical ventilation does not seem to improve survival.

Key words Aspergillosis · Intensive care · Respiratory failure

Introduction

Invasive aspergillosis, a disease caused by tissue invasion by the fungus *Aspergillus*, represents one of the most important infections encountered in immunosuppressed patients. In these patients it carries a very high mortality [1]. The disease is rare in non-immunocompromised patients. The results of antifungal treatment are generally better in the non-immunocompromised than in the immunocompromised patient, but success depends on early diagnosis [1, 2]. Establishing the diagnosis is difficult and confirmation is frequently only possible at autopsy. The development of respiratory failure in the disease heralds a particularly poor

outcome. It is not known whether ICU treatment, including mechanical ventilation, improves outcome in this specific setting. To our knowledge, no paper focusing on the results of such treatment has been published. We reviewed the records of 25 patients who required admission to the intensive care unit because of invasive aspergillosis with respiratory failure, to provide further information regarding the outcome of intensive care treatment for this disease. Most of them had hematologic malignancies for which they had received high-dose chemotherapy.

Patients and methods

Patients

We reviewed the records of all the patients who were admitted to our seven-bed Medical Intensive Care Unit with a final diagnosis of invasive aspergillosis between July 1988 and November 1994. Twenty-six patients, 19 male and 7 female, were found. In one male patient the diagnosis had not been made during life, but was only found at autopsy. As this patient had not received any anti-fungal treatment, he was excluded from further analysis. Most patients were referred from the hematology ward where high-dose chemotherapy is given to patients with hematologic malignancies, leading to an average of 200 neutropenic periods of more than 1 week's duration per year. In a recent survey of infectious complications arising during intensive chemotherapy on our hematology ward, the incidence of documented invasive aspergillosis was 7% (13 patients) in 188 neutropenic periods over a period of 18 months. The actual number will be higher, but the diagnosis often cannot be proven (see Discussion). Neutropenia was defined as less than 0.5×10^9 neutrophils per liter. To assess the severity of the acute illness, Acute Physiology And Chronic Health Evaluation II (APACHE II) [3] scores were calculated at the time of admission to the ICU.

Pre-ICU treatment

All 21 patients referred from the hematology ward had received intranasal amphotericin B prophylaxis against colonization by *Aspergillus* species, together with selective decontamination of the digestive tract with ciprofloxacine and fluconazole, and roxitromycin to prevent streptococcal septicemia. Febrile neutropenia in patients after high-dose cytotoxic chemotherapy was treated empirically with broad-spectrum antibiotics (in this case imipenem). In cases of persisting fever and negative cultures, vancomycin was added to the regimen after 72 h. If fever continued for another 72 h or if the infection progressed or a new infection occurred (e.g. in the nasosinoidal region or in the lungs), amphotericin B 0.7 mg/kg per day was added, with or without positive cultures for *Aspergillus* or yeasts. In the above-mentioned survey on 188 neutropenic periods, amphotericin B was initiated in 13% (25 patients). The remaining four patients, referred from non-hematology wards, did not receive routine prophylactic antibiotic therapy, but all were extensively pretreated with broad-pectrum antibiotics.

Imminent respiratory failure or other life-threatening conditions unresponsive to conservative therapy were indications for referral to the ICU only if there seemed to be a reasonable prospect of cure or significant palliation of the underlying illness.

Diagnosis of invasive aspergillosis

Clinical and radiologic findings led to the suspicion of invasive aspergillosis. In most patients the fungus was found in more than one culture or biopsy specimen. The diagnosis was considered proven when histologic evidence of tissue invasion by typical acutely branching hyphae was found in specimens acquired via biopsy, surgical resection or autopsy. A positive culture of *Aspergillus* in normally sterile body fluids, like the pleural or pericardial fluid, was also considered proof of diagnosis. In patients with a typical clinical and radiologic picture of invasive aspergillosis, positive cultures of broncho-alveolar fluid or sputum were regarded as highly suggestive of the diagnosis when there was no evidence of other infectious or non-infectious causes of pulmonary disease. Direct stains of materials for fungus threads were carried out in all cases. Serologic investigations or determinations of *Aspergillus* antigens in the blood, urine or bronchial secretions, as well as in vitro susceptibility testing of *Aspergillus* strains were not routinely performed.

Cultures of transbronchial or maxillary sinus biopsy were positive in three cases, of a surgical specimen in one, of pleural or pericardial fluid in three, of broncho-alevolar lavage (BAL) fluid in 13 and of sputum in 16 cases (see below). In 11 cases autopsy confirmed the diagnosis. According to the above-mentioned criteria, 15 patients had proven invasive aspergillosis, while 10 patients were highly suspected of having the disease. The disease was initially confined to the lungs in all patients. In one patient, however, a diagnosis of invasive maxillary sinus aspergillosis was also made ante mortem via maxillary sinus biopsy.

Treatment of invasive aspergillosis

Upon entry to the ICU, amphotericin B therapy was initiated or continued in a daily dosage of 1.0 mg/kg unless renal or liver function deterioration made an adaptation of the dose necessary (the dosage was decreased to 0.6–0.7 mg/kg per day in five patients after a mean of 10 (2–31) days, data not shown). Only two patients received lipid-based amphotericin B formulations (Amphotericin B-Lipid Complex, ABLC and liposomal amphotericin B, Ambisome), dosage of 5 mg/kg per day, because of the limited availability of these formulations in our hospital at that time. In a minority of patients, itraconazole ($n = 10$), flucytosine ($n = 2$) and rifampin ($n = 1$) or combinations were given as well. Antibiotics were generally not stopped after a positive culture of *Aspergillus* species as long as the patients were neutropenic.

Supportive Care in the ICU

Mechanical ventilation, vasoactive drugs, Swan-Ganz catheterization and kidney replacement therapy, such as intermittent hemodialysis or continuous arteriovenous hemodialysis, were used according to common standards. Maximal supportive care was given until obvious deterioration of the clinical condition of the patient developed, despite optimal antifungal therapy.

Results

Table 1 summarizes the demographic features and underlying diseases of 25 patients with proven or highly suspected invasive aspergillosis, as well as previous (chemo-)therapy. One patient had not received any immunosuppressive therapy. He nearly drowned after a car accident.

Table 1

Patient	Sex	Underlying disease	Age (year)	Last (chemo-)therapy	Reason for admission ICU	Apache II score	Neutrophil count on admission to ICU ($\times 10^9$/l)	Antifungal therapy	Duration of antifungal therapy (days)	Length of stay in ICU (days)	Outcome
1	m	NHL	37	CHOP	Acute renal failure	19	5.5	Ampho B, 5-FC, rifamp	9	22	Died
2	m	TT	22	VIP	Circulatory failure	26	< 0.1	Ampho B	24	24	Died
3	m	SLE	17	Cyclosporine, prednisolone	Resp insuff	21	0.8	Ampho B	1	22	Died
4	m	HCL	53	Alfa-IFN	Resp insuff	20	0.5	Ampho B, itra	17	18	Died
5	m	NHL	33	cCHVP	After resuscitation	30	9.3	Ampho B, itra	44	7	Died
6	m	ALL	61	Vincristine, dauno, asparag., prednisone	Resp insuff	18	1.5	Ampho B, itra	19	10	Died
7	f	CML, BC	44	Vincristine, dauno, asparag., prednisone	Resp insuff	25	< 0.1	Ampho B	1	1	Died
8	m	NHL	24	High dose methylprednisolone, CHOP	Resp insuff	18	0.6	Ampho B	5	36	Died
9	m	NHL	56	IMVP	After resuscitation	50	0.1	Ampho B, itra	1	2	Died
10	m	AML	21	Mitoxantrone-VP-16	Resp insuff	20	< 0.1	Ampho B, itra	58	14	Died
11	m	NHL	59	BEAM, AutoBMT	Resp insuff	29	< 0.1	Ampho B	3	4	Died
12	m	MM	40	Cyclophosphamide, HDM	Resp insuff	23	0.1	Itra, ampho B	15	5	Died
13	m	NDR, ARDS	62	None	Resp insuff	33	8.1*	Ampho B, 5-FC	8	15	Died
14	f	NHL	29	CHOP	Resp insuff	29	< 0.1	Ampho B	1	10	Died
15	m	NHL	45	Cyclophosphamide, HDM	Resp insuff	32	0.1	Ampho B, itra	11	8	Died
16	m	AML	51	Dauno-araC	Massive hemoptysis	9	25.2	Ampho B, itra	16	10	Survived
17	f	NHL	53	BEAM, AutoBMT	Resp insuff	41	0.1	Ampho B, itra	11	4	Died
18	m	MM	53	HDM	Resp insuff	38	0.2	Ampho B	11	5	Died
19	f	AML	52	Dauno-araC	Resp insuff	25	1.2	Ampho B, itra	31	13	Died
20	f	NHL	46	BEAM, AutoBMT	Resp insuff	25	0.3	Ampho B	8	8	Died
21	f	NHL	57	BEAM, AutoBMT	Resp insuff	33	< 0.1	Ampho B	9	4	Died
22	m	MM	57	HDM + PBSCT	Resp insuff	41	0.2*	Ampho B	12	2	Died
23	f	PAN	71	High dose methylprednisolone	Resp insuff	25	13.4*	Ampho B	49	51	Died
24	m	NHL	23	Doxorubicin, cyclophosphamide, methylprednisolone	Resp insuff	32	< 0.1	Ampho B, lip-ampho B	21	24	Died
25	m	AML	63	Dauno-araC	Resp insuff	37	0.4	ABLC®	43	16	Survived
Mean			45			28			17	13	
Standard deviation			15			9			16	12	

* total leukocyte count (*NHL* non Hodgkin lymphoma, *TT* testis teratoma, *SLE* systemic lupus erythematosus, *HCL* hairy cell leukemia, *ALL* acute lymphoblastic leukemia, *CML, BC* chronic myelogenous leukemia, blast crisis, *AML* acute myelogenous leukemia, *MM* multiple myeloma, *NDR, ARDS* near-drowning, adult respiratory distress syndrome, *PAN* polyarteritis nodosa, *CHOP* cyclophosphamide, doxorubicin, vincristine, prednisone, *VIP* etoposide, iphosphamide, cisplatin, *alfa-IFN* alfa-interferon, *cCHVP* cyclophosphamide, daunorubicin, vincristine, prednisone, *dauno*, daunorubicin, *asparag* asparaginase, *IMVP* iphosphamide, methotrexate, vincristine, prednisone, *VP-16* etoposide, *BEAM*, BCNU, etoposide, doxorubicin, melphalan, *AutoBMT* autologous bone marrow transplantation, *HDM* high dose melphalan, *araC* cytosine-arabinoside, *PBSCT* peripheral blood stem cell transplantation, *ampho B* amphotericin B, *rifamp* rifampin, *5-FC* flucytosine, *itra* itraconazole, *lip-ampho B* liposomal amphotericin B, *ABLC* amphotericin B-Lipid Complex)

The reasons for admission to the ICU, length of stay, APACHE II scores, neutrophil counts on admission to ICU and outcome are also shown. In all six patients where a Swan-Ganz catheter was placed, a hyperdynamic profile consisting of a low peripheral systemic resistance and high cardiac output was found. All patients were mechanically ventilated, except one (patient 19) who had a Venturi mask on 100% oxygen. Acute renal failure, making hemodialysis necessary, occurred in eight patients. The mortality was 23 of 25 patients (92%): 20 of 22 (91%) in patients after intensive chemotherapy and three of three (100%) in non-malignant diseases. They all died on the ventilator or within 24 h after extubation, except patient 19 who was never intubated.

The two patients who survived both had acute myelogenous leukemia (AML). The first patient (no. 16) had already been discharged from hospital after his first cycle of chemotherapy and was not neutropenic anymore. A localized *Aspergillus* infection in the upper lobe of the left lung had invaded the left subclavian artery, which led to the formation of an aneurysm. Rupture of the aneurysm into the lung resulted in massive hemoptysis. Lobectomy with aneurysmectomy could be performed. The pathologic specimen showed fungal pneumonia in the left upper lobe with infiltration of *Aspergillus* species in the vessel wall. Mechanical ventilation took place only in the perioperative phase. He had the lowest APACHE II score in this series. The other patient who survived (no. 25) had received his second cycle of induction chemotherapy. Because of an infiltrative lesion in the right upper lobe during the preceding course of chemotherapy, he was given his second cycle under prophylaxis with amphotericin B, 0.7 mg/kg per day. However, he developed extensive bilateral pulmonary infiltrations with respiratory failure. Computed tomography of the thorax showed cavitating spherical masses with "halo phenomena" and wedge-shaped densities through both lungs, compatible with the classic picture of invasive aspergillosis. Sputum cultures revealed *Aspergillus* species, but bronchial washings remained negative. Although the APACHE II score upon admission to the ICU was very high, treatment with high dose amphotericin B in the form of ABLC, 5 mg/kg per day and broad-spectrum antibiotics was effective.

Fifteen patients were deeply neutropenic at the time of admission to the ICU (Table 1). The mean duration of neutropenia was long: almost 3 weeks (20 $\pm$ 14 days, excluding the two patients with near-drowning and polyarteritis nodosa (PAN), respectively). Diagnosis was made after a mean of 18 ($\pm$ 14) days after the 1st day of neutropenia, 25 ($\pm$ 10) days after the initiation of immunosuppressive therapy, while patients had symptoms for 17 ($\pm$ 12) days. In the patients who died, survival was less than 1.5 weeks after the diagnosis was made. Twelve of them had already recovered from neutropenia for a mean of 13 ($\pm$ 9) days at the time of death (data not shown).

Table 1 also provides the types and duration of antifungal treatment. The microbiologic information is given in Table 2. On a total number of 22 cultures of bronchial washings, 13 (59%) yielded *Aspergillus*. Also, of 74 sputum cultures, 44 (59%) were positive for *Aspergillus* (data not shown). Concomitant infections are shown in Table 2 as well. In patients 12, 13 and 24, infections with *Pseudomonas putida*, *Pseudallescheria boydii* and *Pseudomonas aeruginosa*, respectively, probably contributed to death. Table 3 summarizes the causes of death and, if performed, the results of autopsy (11 patients). In patients where no Swan-Ganz catheter was placed, the causes of death were clinically determined or retrospectively, on the basis of autopsy findings. In all autopsied cases invasive aspergillosis was found. In eight of them the disease had disseminated to various organs.

Discussion

Mortality from invasive pulmonary aspergillosis in neutropenic patients has been reported in small series only, and varied between 13 and 100%, depending on the duration of neutropenia [1, 4]. In non-immunocompromised patients, the success of antifungal treatment depends on early diagnosis. Early treatment is generally effective [1]. Delay in diagnosis is the rule, however, so therapy is not initiated and previously immunocompetent patients may die from the disease. In a report of 25 proven cases in non-neutropenic, non-immunocompromised patients, only one survived. In the majority, the diagnosis was made at autopsy and was not suspected during life [2]. Reports on the impact of ICU treatment in invasive aspergillosis have not been published before.

In our series of 25 patients, with 15 proven and 10 highly probable cases, the mortality rate was 92%, even with maximal supportive care. Only two patients survived. One had a localized infection while not being neutropenic anymore. The other received prophylactic amphotericin B therapy. He was recovering from neutropenia at the time of admission to the ICU. However, in our series, rising neutrophil counts did not generally predict a favorable outcome: 12 patients had had normal neutrophil counts for a mean of 2 weeks at the time of their death. In our three patients with non-neoplastic diseases, of which two were without neutropenia, the mortality was even 100%. In four patients (no. 1, 8, 13 and possibly no. 3) invasive aspergillosis appears to have developed only after their admission to the ICU. None was in neutropenia at that time and one patient

Table 2

Patient	Diagnosis made by culture or histology of	Certainty of diagnosis	Direct stain: hyphae	*Aspergillus* species	Concomitant infections
1	Sputum	Highly suspected	neg.	Undetermined	*S. aureus* in blood culture 1 month before death
2	Sputum	Highly suspected	neg.	*fumigatus*	*Acinetobacter* in sputum 2 weeks before death
3	Autopsy	Proven	neg.	Undetermined	*Acinetobacter* spp cultured from lung post mortem
4	BAL, sputum, autopsy	Proven	pos.	*fumigatus*	*E. coli* in blood culture 2 days before death
5	Sputum	Highly suspected	neg.	Undetermined	*E. cloacae* in BAL 1 week before death
6	Pleural effusion, BAL, autopsy	Proven	neg.	*fumigatus*	None found
7	BAL, sputum, autopsy	Proven	pos.	*fumigatus*	*Streptococcius viridans* in blood culture 3 weeks before death
8	Sputum, autopsy	Proven	pos.	*fumigatus, terreus*	None found
9	Transbronchial biopsy, BAL	Proven	pos.	*fumigatus*	Yeast (not *C. alb*) in BAL 1 day before death
10	BAL, sputum, maxill. sinus biopsy	Proven	pos.	*fumigatus*	None found
11	Transbronchial biopsy, BAL, sputum, autopsy	Proven	pos.	*fumigatus*	Yeast (not *C. alb*) in BAL 3 days before death
12	Pericardial effusion , BAL, autopsy	Proven	neg.	*fumigatus*	*Streptococcus viridans* in blood culture 1 month before death, *Pseudomonas putida* cultured from spleen and lung after death
13	Sputum, autopsy	Proven	neg.	*fumigatus, flavus*	*Bacillus* spp in blood culture 2 weeks before death; yeast (not *C. alb.*) and *Pseudallescheria boydii* cultured from lung after death
14	Sputum	Highly suspected	neg.	*fumigatus*	None found
15	BAL, sputum	Highly suspected	pos.	*fumigatus*	*S. pneumoniae* in blood culture 4 weeks before death; yeast, (not *C. alb*) in BAL 1 day before death
16	Resected subclavian artery aneurysm	Proven	neg.	Undetermined	None found
17	BAL	Highly suspected	pos.	*fumigatus*	None found
18	BAL	Highly suspected	neg.	*fumigatus*	None found
19	Pericardial effusion, sputum	Proven	neg.	*terreus*	None found
20	BAL, autopsy	Proven	neg.	*fumigatus*	None found
21	Autopsy	Proven	neg.	*fumigatus*	None found
22	Sputum	Highly suspected	neg.	*fumigatus*	None found
23	BAL, sputum	Highly suspected	neg.	*fumigatus*	None found
24	BAL, sputum, autopsy	Proven	pos.	*fumigatus*	*Ps. aeruginosa* cultured from spleen after death
25	Sputum	Highly suspected	neg.	Undetermined	None found

(*C.alb.* Candida albicans *BAL* bronchoalveolar lavage)

never received any immunosuppressive therapy. Although invasive aspergillosis was probably not the reason for their admission to the ICU, still, mortality in these four patients was 100%.

These results are similar to those in the above-mentioned reports. They are comparable with those reported by others in patients with hematologic and other malignancies on mechanical ventilation [5–16], but worse than in non-immunocompromised patients, who needed prolonged mechanical ventilation for respiratory failure due to various causes [17] (no cases of aspergillosis included).

Some authors were able to identify risk factors for poor outcome in hematologic patients who had to be admitted to the ICU because of respiratory failure [9–11, 16]. In a recent study of 193 bone marrow transplantation recipients (allogeneic and autologous), Faber-Langendoen et al. state that mechanical ventilation is futile in patients over 40 years of age or within 90 days after transplantation, regardless of the cause of respiratory failure [13]. Others mention an Apache score of greater than 30, the dysfunction of an increasing number of organ systems, failure to recover marrow function after chemotherapy

Table 3

Patient	Cause of death	Autopsy findings
1	Massive hemoptysis	Not performed
2	Septic shock	Not performed
3	MOF	Aspergillosis lungs, pleura, perimyocardium, perirenal, perforating duodenal ulcer, brain, meninges
4	Massive pulmonary hemorrhage	Aspergillosis lungs, pleura, perimyocardium, perirenal, perforating ulcus duodeni, brain, meninges
5	Massive pulmonary hemorrhage	Not performed
6	Septic shock	Aspergillosis lungs, myocardium, epicardium, kidneys, brain and meninges
7	Massive pulmonary hemorrhage	Aspergillosis lungs, stomach and duodenum (ulcers), spleen. Brain: no Aspergillosis
8	MOF	Aspergillosis lungs, esophagus, stomach and duodenum (ulcers). Brain: no Aspergillosis
9	Irreversible shock (cardiogenic?)	Not performed
10	Septic shock	Not performed
11	Septic shock	Aspergillosis lungs, no brain section
12	Septic shock	Aspergillosis lungs, pericardium, left kidney. No brain section. Also: pseudomonas in lungs and spleen
13	MOF	Aspergillosis lungs, epicardium, myocardium, endocardium, kidneys, left adrenal gland, brain and meninges
14	Septic shock	Not performed
15	Irreversible shock	Not performed
16	(a)	(a)
17	Septic shock	Not performed
18	Septic shock	Not performed
19	Cardiogenic shock	Not performed
20	MOF	Aspergillosis lungs, no brain section
21	Septic shock	Aspergillosis lungs, pleura, pericardium
22	Septic shock	Not performed
23	Resp. insufficiency	Not performed
24	MOF	Aspergillosis lungs, pseudomonas in spleen
25	(a)	(a)

(*MOF* multi-organ failure, (*a*) survived)

and unresponsive malignant disease as indicators of such a poor prognosis that patients with these features should probably not be mechanically ventilated [14, 16]. Infectious causes and duration of mechanical ventilation longer than 4 days were invariably associated with fatal outcome in other studies [5, 18]. Not all reports confirm these findings [12, 15]. In our study, the number of survivors seems to be too low to make adequate analyses concerning risk factors for prognosis in invasive aspergillosis with respiratory failure.

Ante mortem confirmation of the diagnosis is one of the greatest problems in invasive aspergillosis. Lung biopsy can establish the presence of the disease [19, 20], but this is a procedure one wishes to avoid in patients with pancytopenia. Above all, it does not seem to improve outcome [16, 19]. A positive culture of sputum could just reflect colonization, but may be considered highly suggestive of invasive aspergillosis in circumstances of longstanding neutropenia and a compatible clinical and X-ray picture [20, 21]. However, according to the literature, sputum samples fail to yield *Aspergillus* in most patients and cultures of BAL fluid also frequently give negative results [22, 23]. We, nevertheless, found positive cultures in 59% of both BAL and sputum cultures. In most cases multiple specimens were taken at different times. Recent advances in the detection of *Aspergillus* include determinations of *Aspergillus* antigens in BAL fluid, serum or urine, polymerase chain reaction (PCR) of BAL being the latest asset [24]. Serology in aspergillosis seems disappointing, however, because of the poor antibody response, especially in immunosuppressed patients [8, 25].

In 22 (88%) of our patients, the diagnoses could be confirmed or at least established as very likely only after admission to the ICU. Aspiration of sputum and bronchoscopy with BAL or biopsy could be performed much more easily and safely in circumstances of adequate cardiopulmonary monitoring and support than

on a hospital ward. Other causes of diffuse pulmonary infiltration could be excluded at the same time. We doubt, however, whether this implied any therapeutic benefit, considering the overall poor results of ICU treatment in our group.

It is clear that we need more effective therapy for invasive aspergillosis, so that we may be able to prevent the development of respiratory failure. Itraconazole is reported to be at least as effective as amphotericin B in invasive aspergillosis [26–28]. For ICU use, it has the disadvantage of being available only in an enteral form. Regular measurements of plasma concentrations are desirable [28]. New triazole drugs with good in vitro activity against *Aspergillus* species are on their way, but not yet available for clinical practice. Lipid-based formulations of amphotericin B, like liposomal amphotericin B or Amphotericin B-Lipid-Complex, seem promising [29]. However, since prolonged granulocytopenia is considered the major risk factor for invasive aspergillosis [30], the addition of hematopoietic growth factors to chemotherapy schemes leading to a shorter period of neutropenia might be an effective strategy in preventing invasive aspergillosis. Other prophylactic measures like high efficiency particulate air-type filters have also proven their usefulness [31].

In conclusion, the admission of patients with presumed invasive aspergillosis and respiratory insufficiency to an ICU leads to an improvement of diagnostic certainty in almost all cases. It should be considered in cases of localized infection and when obvious signs of hematologic recovery exist. In all other situations, ICU treatment and mechanical ventilation in invasive aspergillosis do not seem to improve outcome. It should therefore only be initiated with utmost restraint in these circumstances. Also, the development of invasive aspergillosis on the intensive care unit appears invariably fatal. However, our results are obtained in a relatively small number of patients and our conclusions can only be drawn for the treatment modalities that were used in this group. In the event of emerging new therapeutic approaches, a reappraisal of ICU treatment of invasive aspergillosis should be considered.

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